UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/827,666	04/06/2001	Timothy J. Neuberger	365279-001	6738

23565 7590 06/14/2005

KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,666	NEUBERGER ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-12,19-31,34-51,55-74* is/are pending in the application.

4a) Of the above claim(s) *29-31,37-45 and 59-66* is/are withdrawn from consideration.

5)☐ Claim(s) *73, 74* is/are allowed.

6)☒ Claim(s) *8-12,19-28,34-36,46-51,55-58 and 67-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary of Action

1. The rejection of the claims 8-12, 19-28, 34-36, 46-51, 55-58 and 67-72 under 35 USC 112, first paragraph, is maintained for the reasons of record.

2. The rejection 8-12, 19-23, 57, 67 and 69-72 under 35 USC 102(b) as being anticipated by Nair et al. (US 4965284) is maintained for the reasons of record.

Status of Application

3. By Amendment filed November 08, 2004, claims 52-54 have been cancelled; claims 8, 10, 12, 19, 21, 22, 25, 27, 34, 46-47, 50 and 57 have been amended; and claims 73 and 74 have been newly added. Claims 8-12, 19-28, 34-36, 46-51, 55-58 and 67-74 are currently pending for prosecution on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8-12, 19-28, 34-36, 46-51, 55-58 and 67-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF or NF-PO4 in the bone marrow or neural cells", "promoting growth or differentiation of growth and differentiation of neural precursor cells" or "treating spinal cord injury by administering bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide-treated animal to a site of injury in animal", does not

reasonably provide enablement for "promoting neural cell growth or differentiation", "promoting recovery of cells expressing neuronal progenitor cell markers after injury to the neuronal cells", "promoting neural cell growth or differentiation of neural cells" and "treating injury to neuronal cells", with the administration of compounds of formula (II). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are:(1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; (8) the breadth of the claims When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant specification discloses that the instant invention relates to promoting neural tissue regeneration or neural expression. The specification defines neural tissue as "all tissue endogenous to the nervous system" (page 13, lines 10-12 and lines 22-26); neural expression as the expression of any proteins indicative of neural tissue growth or neural tissue cell differentiation from progenitor cells (page 13, lines 13-18); and neural progenitor cells as "any cell that can differentiate into a neural tissue cell, or be induced to differentiate into a neural tissue cell, including neural precursor cells, whether directly or through intermediate cell stages"

(page 14, lines 1-3). As the specific embodiments of the invention, the instant specification discloses in-vitro study testing the activity of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide in increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF and NF-PO4 (Examples 1 and 2) and in-vitro study testing the activity of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide in increasing the growth of neurons or astrocytes (Example 4). The instant specification also discloses that animals (Fischer F344 female rats) treated with bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide-treated donor animal demonstrates a decrease in cavity size at the contusion injury site, in vivo study (Example 3).

The specification does not provide sufficient guidance for the skilled artisan how to ascertain (i) which proteins indicative of neural tissue growth or neural tissue cell differentiation from progenitor cells other than the disclosed eNCAM, MAP II, beta-tubulin, nestin, NF and NF-PO4, and (ii) which neural tissues, neural precursor cells or progenitor cells other than bone marrow cells would be enabled in this invention in animals or human. Furthermore, the specification does not provide sufficient guidance for the skilled artisan how to ascertain that (iii) the growth of neuron or astrocytes by the administration of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide in vitro would lead to the improvement of the functional recovery of neurons, and (iv) provide the effective treatment of complex neurodegenerative diseases or conditions that may have unrelated manifestation in vivo, without undue amount of experimentation.

The instant invention relates to method of promoting neural cell growth or differentiation (claims 8-12, 34-36, 67-68); a method for promoting recovery of cells expressing neuronal

progenitor cell markers after injury to the neuronal cells (claims 19-28); a method for treating injury to neuronal cells (claims 46-51, 55-56); a method for promoting growth and differentiation of neural precursor cells (claims 57-58), wherein methods requires the administration of compounds of formula II. More specifically, claims 34-36 and 57-58 are directed to transplantation method.

The prior art recognizes the treatment of spinal cord injury by replacing damaged neural tissue with transformed cells of neural and non-neural origins, neutralizing the nerve-growth inhibitory properties of various proteins in the CNS environment, as well as introduction of stem cells or progenitor cells.

The relative skill of those in the art of pharmaceuticals is high. The unpredictability of the pharmaceutical art is very high. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the claimed utility of the instant compounds.

As stated above, with the exception of "method of increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF or NF-PO4", "promoting growth or differentiation of growth and differentiation of neural precursor cells" with the transplantation method described in claim 57 or "treating spinal cord injury by administering bone marrow cells from N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide-treated animal to a site of injury in animal", the skilled artisan cannot envision that (a) the administration of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide is capable of increasing the expression of other known neural proteins (e.g., vimentin, Sox2, Ki-67, GD2 ganglioside, MAP2ab, NeuN, FMRP, Tau, GFAP, dublecortin, CD133, CD44, CD81, CD90, CD29, NumA and etc...), and (b) promoting regeneration of diverse neural tissues, neural precursor cells, progenitor cells or tissue of neural origin (e.g., schwanne cells,

stems cells, oligodendrites, etc...) in animals or human; and (c) the administration of N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide, without neutralizing the nerve-growth inhibitory properties of various proteins in the CNS environment, is capable of providing the desired effects of the claimed invention, particularly claims 8-12, 19-28, 46-56 and 67-72 where no transplantation method is required, in animals or human.

The breath of the instant claims encompasses promotion of neural cells (e.g., stem cells, progenitor cells, neurons, glial cells, astrocytes, oligodendrites, etc...), the expression of neural proteins (e.g., eNCAM, MAP II, beta-tubulin, nestin, NF and NF-PO4, vimentin, Sox2, Ki-67, GD2 ganglioside, MAP2ab, NeuN, FMRP, Tau, GFAP, dublecortin, CD133, CD44, CD81, CD90, CD29, NumA and etc...) or the treatment of complex neurodegenerative conditions (e.g., multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, diabetes, senile dementia, dysplasia, myelitis, spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, mitochondrial multi.system disorder, transverse myelitis, anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy, Down's Syndrome in middle age, Diffuse Lewy body disease, Wernicke-Korsakoff syndrome, chronic alcoholism; Creutzfeldt-Jakob disease, Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease, Dementia pugilistica, etc...), that are known today, and those that may be discovered in the future.

For the reason given above, in view of the nature of the invention, the amount of guidance present in the specification, the breath of the claims, the relative skill of those in the art,

and the predictability or unpredictability of the art, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 8-12, 19-23, 57, 67 and 69-72 are rejected under 35 U.S.C. 102(b) as being anticipated by Nair et al. (US 4965284).

Nair teaches the use of the claimed compounds including N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide for modulating the immune system; stimulating the proliferation and differentiation of blood cell progenitors in bone marrow of warm-blooded animals (ultimately for human); accelerating the recovery of white blood cell progenitors in bone marrow of warm-blooded animals; and enhancing the activity of immune cells and/or immunoregulatory proteins, wherein said compound (composition containing said compound) is administered to warm-blood animal or warm-blood animals conditioned to chemical or irradiation therapy in amounts ranging from about 5 mg to about 400mg/kg of body weight per day, preferably from about 25mg to abut 500mg/kg of body weight per day (column 8, lines para. 1; column 12, lines 60-66; claims, especially claims 16-23).

Although Nair is silent about the instantly required " promoting neural tissue regeneration or expression" (claim 8); "the tissue is of neuronal origin and the method is for promoting neural

expression" (claim 10); "the administration is effective to promote the neural expression of one or more proteins selected from the group consisting of: eNCAM, MAP II, beta-tubulin, nestin, NF and NF-PO4" (claim 12); "promoting recovery of behavioral function of neurons after a decrease in neural function" (claim 19); and "promoting regeneration of neural precursor cells" (claim 57), such properties or characteristic deem to be inherently presented in the referenced method. Where the administration of same compound (i.e., N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide) at overlapping dosage amounts (i.e., about 5 mg to about 400mg/kg of body weight per day, preferably from about 25mg to abut 500mg/kg of body weight per day) to same treatment population (i.e., "warm blooded animal", "warm blooded animal" conditioned to "chemical or irradiation therapy"), the instantly claimed mechanism of action must be inherently presented in the prior art (Nair). Therefore, Nair anticipates the claimed invention.

Response to Arguments

6. Applicant's arguments/Declaration filed November 8, 2004 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that the submitted data support the use of the compounds of the present invention to promote the growth and differentiation of neuronal progenitor cells. Applicant alleges that based on the submitted data the instantly claimed method of promoting neural cell growth or differentiation is enabled.

This argument is found unpersuasive. Although the Examiner agrees with Applicant that the growth and differentiation of neuronal precursor cells from a stem cell derived from neural cells or bone marrow cells are known in the art, there is no indication in the instant claims

(claims 8-12, 34-36, 67-68) that the administration of the claimed composition is going to promote neuronal precursor cells. Unlike the applicant's argument, the claims are directed to a method of promoting neural cell growth or differentiation. The specification provides insufficient guidance to support the genus encompassed by the claims.

Applicant's argument in the response takes the position that a skilled artisan would be able to use the structure of the specific compound tested in the present application to develop analogs (such as those taught by the instant application) having similar biological activity. Applicant alleges that routine screening for similar compounds that promote nerve cell growth or differentiation could routinely be performed by the skilled artisan. Thus, it would be expected that other compounds having a similar structure would have similar biological activity.

This argument is found persuasive. Accordingly, the Examiner withdraws the rejection under 35 USC 112 with respect to this issue.

Applicant's argument in the response takes the position that it is apparent from the literature presented (Chiba et al., Parati et al., Riess et al. and Zhao et al.) that neural stem/precursor cells are capable of restoring neuronal function in various models of neurodegenerative diseases and conditions, including traumatic brain injury, spinal cord injury, stroke and Parkinson's disease.

This argument is found unpersuasive. Unlike Applicant's argument, the supplied references are directed to transplantation of neural stem/precursor cells to injured animals suffering from traumatic brain injury, spinal cord injury, stroke or Parkinson's disease. There is

no indication in the instant claims (8-12, 19-28, 46-51, 55-56, 67-68) that neural stem/precursor cells are transplanted to the injured animals. Thus, the skilled artisan cannot envision whether the direct administration of said compounds to mammals would be capable of promoting growth or differentiation of neural cells.

In addition, although the supplied references shows possible application in the treatment of traumatic brain injury, spinal cord injury, stroke or Parkinson's disease, there is no demonstrated correlation that the tests and results apply to all of the disorders embraced by the instant claims, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, diabetes, senile dementia, dysplasia, myelitis, spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, mitochondrial multi.system disorder, transverse myelitis, anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy, Down's Syndrome in middle age, Diffuse Lewy body disease, Wernicke-Korsakoff syndrome, chronic alcoholism; Creutzfeldt-Jakob disease, Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease and Dementia pugilistica.

Applicant's argument in the response takes the position that Nair et al. do not teach or suggest the use of the genus of compounds represented by the formula for the instantly claimed method.

This argument is found unpersuasive. It is noted that the disclosure of a species, N-[4-[(4-fluorophenyl)sulfonyl]phenyl]-acetamide, anticipates a claim to a genus containing that species.

See In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989) (Gosteli claimed a genus of 21 specific chemical species of bicyclic thia-aza compounds in Markush claims. The prior art reference applied against the claims disclosed two of the chemical species. The parties agreed that the prior art species would anticipate the claims unless applicant was entitled to his foreign priority date.).

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Claims 73 and 74 are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600